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Chia-Wen Chien[1], Ming-Chang Chiang[2], I-Ching Ho[3], and Te-Chang Lee[1,3]

[1]Institute of Biopharmaceutical Science, National Yang Ming University, Taipei, Taiwan 11266; [2]Department of Life Science, National Central University, Taoyuan, Taiwan 32054; [3]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan 11529, R. O. C.

Address correspondence to Dr. Te-Chang Lee, Institute of Pharmaceutical Science, National Yang Ming University, Pei-Tou, Taipei 112, Taiwan, Republic of China. Telephone: 886-2-28267300; Fax: 886-2-28237583. E-mail: tclee@ym.edu.tw.

Running Title: Chromosomal alterations in arsenite-induced tumorigenic HaCaT cells

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Abbreviations:

CGH = comparative genomic hybridization

CIN = chromosomal instability

MN = micronuclei

SRB = sulforhodamine B

Outline of section headers: Abstract, Introduction, Materials and Methods, Results, Discussion, References.

Abstract

Inorganic arsenic is a well-documented human carcinogen. Chronic low dose exposure to inorganic arsenic is associated with an increased incidence of a variety of cancers, including skin, lung, bladder, and liver cancer. Since genetic alterations often occur during cancer development, the objective of this study was to explore what types of genetic alterations were induced by chronic exposure of human HaCaT cells to arsenic. After 20 passages in the presence of inorganic trivalent arsenite at concentrations of 0.5 or 1 μM, HaCaT cells had higher intracellular levels of glutathione, became more resistance to arsenite, and showed an increased frequency of micronuclei. Furthermore, the previously non-tumorigenic HaCaT cells became tumorigenic, as shown by subcutaneous injection into Balb/c nude mice. Cell lines derived from the tumors formed by injection of arsenite-exposed HaCaT cells into nude mice expressed higher levels of keratin 6, a proliferation marker of keratinocytes, than parental HaCaT cells, whereas the expression of keratins 5, 8, and 10 was significantly decreased. Comparative genomic hybridization demonstrated chromosomal alterations in the 11 cell lines derived from these tumors; all 11 showed significant loss of chromosome 9q and 7 showed significant gain of chromosome 4q. The present results show that long-term exposure to low doses of arsenite transformed non-tumorigenic human keratinocytes to cells that were tumorigenic in nude mice and

that chromosomal alterations were observed in all cell lines established from the tumors.